Inhibition of complement activation in cardiac surgery

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In this issue of the *Journal*, Carrier and colleagues[1] report on a subgroup analysis of the PRIMO-CABG study,* in which patients undergoing combined coronary artery bypass grafting (CABG) and aortic valve replacement receive either placebo or the complement C5-binding monoclonal antibody pexelizumab. The initial phase II prospective multicenter trial on the use of pexelizumab during coronary and valve surgery in 914 patients[2] found no significant effect on mortality. Post hoc analysis, however, suggested that for isolated CABG, pexelizumab did reduce death or myocardial infarction. Some of the same investigators published the benefit of pexelizumab on cognitive decline and stroke after CABG. The authors reported no differences, except for a slight improvement in the visuo-spatial domain.[3] The PRIMO-CABG study was a multi-institutional, randomized trial evaluating a complement C5-binding monoclonal antibody in 3099 cardiac surgery patients with regard to combined mortality or myocardial infarction. The primary end point within 30 days after surgery was reduced by about 20% in patients with isolated CABG treated with pexelizumab compared with control patients.[4] In the current article, the authors continue their series of studies of patients who are part of the same trial of the complement-binding protein in cardiac surgery in which cardiopulmonary bypass is used. The current study clearly demonstrates a benefit of pexelizumab in reducing both 30-day (3.8% vs 9.9%) and 180-day (5.7% vs 14.4%) mortality in this select, and presumably high-risk, group of patients.

Complement evolved to fight bacterial and other types of infection in a hostile environment. When man was swinging through trees and being chased by tigers, infection and bleeding were the major causes of death. In the modern era, bleeding usually occurs during surgery or after being shot or stabbed, and infection occurs less often. It does often occur in patients who undergo surgery and especially cardiac surgery. During cardiopulmonary bypass, complement is activated owing to antigen-antibody interaction or ischemia-reperfusion (classical pathway) and by contact of blood with foreign substances (alternative pathway). In addition, complement can be activated after contact of blood with microbial surfaces in the recently discovered lectin pathway. Although an exhaustive description of the complement system is not here described, two of the main players in complement activation are C5, which cleaves to the very chemotactic fragment C5a, and C5b, which leads to formation of the terminal membrane attack complex C5b-9. C5b-9 is proteolytic and causes direct tissue injury.

The prevention of this cleavage of C5 by binding C5 with a monoclonal antibody is the theoretical basis for why pexelizumab should work. Instead of being life saving, complement activation during cardiopulmonary bypass may actually decrease the likelihood of an uneventful recovery and lead to myocardial infarction, lung injury, or stroke.

Prospective, randomized, double-blind, placebo-controlled, multicenter trials are difficult, labor intensive, and expensive to carry out. Such clinical investigations as the one described in this article should be encouraged. Industry sponsors desire valid documentation of efficacy and academic investigators desire and deserve credit for their work. In part because of a desire to report positive results, there is a temptation in large, multicenter trials to go back and "post hoc" analyze multiple different groups. The authors are very qualified clinical investigators, and they understand that the primary and secondary end points must be identified before the study is

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initiated. The primary end point in the PRIMO-CABG trial was "composite of death, myocardial infarction, or both at postoperative day 30 in patients undergoing coronary artery bypass grafting without valve surgery." The authors make the point that valve-CABG patients were not included in the primary population and therefore separate analysis of death and myocardial infarction of the 218 patients undergoing combined aortic valve replacement and CABG is permissible.

Another issue that arises from this study relates to the optimal selection of end points. The ideal end point is clinically relevant, objectively ascertained, and occurs at a sufficient frequency in the study population so as to allow the design of an adequately powered clinical trial without breaking the budget. Unfortunately, such end points rarely exist. The result is composite end points that often combine clinically significant or hard end points, which occur at a low frequency with less clinically important end points (soft end points), which are more common. Increasingly, surrogate end points consisting of biomarkers, functional assessments, or quality of life measurements are taking the place of or being combined with traditional hard clinical end points. In this study, the pre-specified composite end point consisted of all-cause mortality and myocardial infarction. Although a difference in mortality is unarguably of clinical importance, a difference in perioperative creatine kinase MB elevation is less so. In such situations in which the components of the composite end point carry unequal "weight," the differences in composite end points become more difficult to interpret. The optimal composite end point, therefore, would be one in which the components carry roughly equal clinical "weight," that is, are of equal clinical significance.

Furthermore, the end points need to be tailored to the patient population as well as the disease mechanism being studied. For example, when a drug that prevents ischemia-reperfusion and inflammatory myocardial injury is being evaluated, myocardial infarction is a "cleaner" end point in patients undergoing isolated valve surgery; that is, it is not confounded by other determinants of myocardial infarction like extent and diffuseness of coronary disease, types of grafts used, or history of myocardial infarction. In a group of patients undergoing CABG in addition to valve surgery, these and other confounders that can affect the rates of perioperative myocardial injury may not be equally distributed among the treatment and control groups, particularly when the sample size is relatively small. In the present study, there are statistically nonsignificant but potentially important differences in New York Heart Association class status, prior myocardial infarction, and number of grafts per patient. In addition, certain other patient- and disease-related variables that are not reported or measured may differ between groups. This, again, reinforces the need to pre-specify the subgroups and end points that are to be analyzed at the design stage, ensuring that a large enough sample size exists to allow the results of these subgroup analyses to be meaningful and generalizable.

Finally, the question must be raised as to whether such a drug is necessary to improve the outcome of patients after complex cardiac operations during which time the patient is subjected to cardiopulmonary bypass. For most low-risk cardiac procedures, patients will not likely benefit. However, for very ill patients undergoing prolonged, complicated operations, selective inhibition of complement may improve the outcome, as demonstrated in the present study. In these days when hospital administrators keep track of costs of doing cardiac surgery, the cost of pexelizumab will no doubt affect how often it is administered. Clearly not everyone will receive it at even a modest incremental cost, but at very high cost, very few will receive the drug. The efficacy, as determined by the results of the recently completed PRIMO-CABG II trial, in which additional patients were enrolled, and the cost of the drug, will determine the place of pexelizumab in the treatment of patients having cardiac surgery and in the market.

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